areas or subareas of adjacent labeled regions.) All connections between stages are bidirectional, providing feedforward as well as feedback.

In the course of new or recently acquired behavior, sensory information is processed along the sensory hierarchy—both serially and in parallel. In the cortex, that information translates into action, which is processed down the motor hierarchy to produce change in the environment, which leads to sensory change, which is processed through the sensory hierarchy and then modulates further action, and so on. The prefrontal and posterior association cortices are in the cycle inasmuch and for as long as the behavior contains novelty, uncertainty, or ambiguity and has to bridge time spans with short-term memory. As those constraints disappear and behavior becomes automatic (e.g., walking, skilled routines), the action is integrated in lower structures (e.g., premotor cortex, basal ganglia) and sensory processing shunted at lower levels of the cycle.

Asaad et al. (1998 [this issue of *Neuron*]) take us closer than ever before to understanding how those action-related associations are formed in the prefrontal cortex, at the top of the cycle. Their experimental animal, a monkey, is trained in a delay task, where a particular visual stimulus calls for a particular movement of the eyes after a short delay. This delay makes the task a memory task, requiring the subject to recognize and retain a stimulus for subsequent action. Based on previous research, so-called memory cells are expectedly found, which fire faster during the delay than during intertrial baseline periods; the discharge of some of these cells is stimulus preferential, that is, higher in reaction to a given stimulus than to another. In other cells nearby, the discharge is related to the movement. Most notable is the finding of cells that are related to both the cue and the response, or a particular combination of the two. As the learning of a new association progresses, activity in prefrontal cells related to the direction of impending movement develops progressively earlier. Thus, the authors demonstrate in an elegant manner that prefrontal neurons become part of cortical networks containing and representing associations between visual stimuli and movements.

Because memory cells were observed first in the prefrontal cortex and repeatedly reencountered in it (Fuster and Alexander, 1971; Niki, 1974; Funahashi et al., 1989), such cells have long been considered the substrate of its specific role in working memory. There is now ample evidence, however, that this state of memory activates also other broad and widely dispersed areas of the cortex with which the prefrontal cortex is connected. In addition to prefrontal neurons, the short-term retention of visual stimuli elicits the sustained activation of neurons in inferotemporal cortex (Fuster and Jervey, 1981; Miller et al., 1993) and even in somatosensory cortex if the task is visuo-haptic (Zhou and Fuster, 1997). In sum, therefore, the memory-active prefrontal cells are part of extensive networks that span posterior as well as frontal cortex. There is evidence that their sustained activation in working memory results from the dynamic interactions between those cortices at or near the top of the perception–action cycle (Fuster, 1997a). The cells that Asaad et al. describe seem to become part of those networks as they are formed or expanded by learning and thus also to become engaged in the interactions at the summit of the perception–action cycle. In general, however, as sensory–motor associations become routine, they are presumably relegated to lower stages of the cycle. That is probably why, with overlearning, cortical activations disappear from tomographic screens, and the neurons described by Asaad et al. seem to lose their interest in old or familiar associations. The experimental approach of these investigators is uniquely suited to reveal these changes. Indeed, somewhat paradoxically, the microelectrode remains the best tool to explore neural mechanisms in distributed cortical networks with thousands if not millions of neurons.

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Touch Channels Sense Blood Pressure

Although we can all cite examples of individuals that seem to operate without perfusing their brains, this is just an illusion. Nature has installed pressure sensors (baroreceptors) to ensure relatively constant blood flow through their arteries. Imbedded in the walls of the arch of the aorta and the carotid sinus, arterial baroreceptor nerve termini form intricate networks that fire in response to changes in blood pressure. These nerves report to the brain stem respiratory centers located in the solitary tract nucleus. In turn, these centers regulate blood vessel tone and heart pumping effectiveness through the sympathetic nervous system. In this issue of *Neuron*, Drummond et al. (1998) provide evidence that the mechanotransducers for the arterial pressure sensors are members of the degenerin (DEG)/ENaC family of cation channels.

Although the baroreceptor reflex is well understood,

little is known about the basic mechanosensory process that senses distension of the arterial wall. Ion channels whose gating is responsive to changes in plasma membrane tension are primary candidates for these mechanotransducers. In the cardiovascular system, mechanosensitive channels have been recorded from endothelial cells lining the lumen of arteries and from cardiac myocytes (reviewed by Sachs and Morris, 1998). The energy needed to gate mechanosensitive channels may be collected by the membrane-associated cytoskeleton. But, to date, the only cloned channel that is an unequivocal mechanosensor is the bacterial MscL protein (reviewed by Sukharev et al., 1997). The bacterial channel is unique in that it is a hexameric protein complex that can be gated by membrane tension independent of cytoskeletal elements.

Our first glimpse at the molecular structure of a mechanosensitive channel in eukaryotes was obtained from genetic studies conducted in the worm *Caenorhabditis elegans*. These worms move away in response to light touch of the nose or body. Using genetic approaches, ~400 mutants were isolated that were defective in the touch response but still capable of locomotion (reviewed by Tvernarakis and Driscoll, 1997). From these mutants, 16 genes were identified that when mutated gave rise to the aberrant mechanosensory phenotype, Mec. The Mec mutations involve proteins localized in a network of six neurons and associated cytoskeletal and extracellular components. These proteins are distributed across the long axis of the worm and comprise what are now known as touch receptors. Interestingly, mutations within a subset of these genes also result in neuronal cell death and are hence also broadly referred to as degenerins (DEG).

A subset of the DEG proteins (MEC-4, MEC-10) share homology with the amiloride-sensitive sodium channel subunits previously described in the epithelial layers of the kidneys, lungs, and intestines of vertebrates (Palmer, 1992). The epithelial amiloride-sensitive sodium channel (ENaC) is a multimeric protein complex composed of three subunits (α, β, and γ), each of which is thought to be represented three times in the channel complex (Snyder et al., 1998). This finding inspired the notion that MEC-4 and MEC-10 comprise subunits of a mechanically gated ion channel related to the amiloride-sensitive epithelial sodium channel, and, indeed, amiloride is known to block certain classes of mechanosensitive channels (Hamill and McBride, 1996). As a family, these proteins have been termed the DEG/ENaC cation channels.

Structurally, each DEG/ENaC channel subunit contains two hydrophobic transmembrane segments, a large extracellular loop containing three cysteine-rich regions, a domain with homology to venom neurotoxins, and cytoplasmic N and C termini through which the channel is thought to associate with the cytoskeleton. Interestingly, the bacterial MscL channel also contains two membrane-spanning domains and cytoplasmic N and C termini. Other MEC proteins include tubulin-based cytoskeletal proteins (MEC-2, MEC-7, MEC-12) and components of the extracellular matrix (MEC-5 and MEC-9). DEG/ENaC homologs also exist in *C. elegans* but are not confined to the touch receptor complexes. UNC-8 and DEL-1 are DEG/ENaC homologs expressed in motor neurons, while UNC-105 is expressed in muscle cells. Mammalian homologs, BNaC1, BNaC2, and DRASIC, have also been cloned from nervous tissue (reviewed by Tvernarakis and Driscoll, 1997; Snyder et al., 1998, and references therein). Mutations near the second transmembrane domain result in the DEG/ENaC channels being constitutively open, allowing the unobstructed entry of cations into the cell. The flood of cations results in degeneration of the mechanosensory neurons of *C. elegans*.

Can the DEG/ENaC channels bridge the mechanosensory gap between arterial blood pressure and baroreceptor discharge? Until recently, the evidence linking baroreceptor mechanotransduction with the DEG/ENaC channels was purely circumstantial. Mechanosensitive gating of the DEG/ENaC channels has not been unequivocally shown in their native tissues, in part due to the relative inaccessibility of the baroreceptive nerve terminals buried within the arterial wall. Nonetheless, mechanosensory responses have been observed from dissociated baroreceptor neurons isolated from the nodose ganglion, which innervates the aortic arch. These responses included macroscopic Ca^{2+} entry in cells in response to membrane distortion by a puff of solution (Sullivan et al., 1997) and single channel cation currents activated by suction applied through a recording electrode (Kraske et al., 1998). Although these responses were blocked by the trivalent gadolinium previously shown to block mechanosensitive channels in other preparations, their sensitivity to amiloride was not demonstrated (Hamill and McBride, 1996). Also, since the site of mechanotransduction is at the nerve terminals imbedded in the arterial wall, the significance of mechanosensitive responses measured on the soma is questionable.

Drummond et al. (1998) use reverse transcriptase polymerase chain reaction (RT–PCR) to show that β and γ subunits of the epithelial amiloride sodium channel (ENaC) are present in isolated baroreceptor cells of the nodose ganglion. Since nodose ganglia contain non-baroreceptor cells, this result was corroborated by immunostaining for γENaC in baroreceptor neurons specifically labeled with the fluorescent lipophilic dye Di-I. Di-I applied to the aortic arch retrogradely labeled a majority (80%) of nodose cells that had also stained positively for γENaC. Anterogradely labeled nodose ganglia stained small nerve terminals in the aortic arch with both Di-I and anti-γENaC, and the labeled nerve terminals had complicated morphologic features previously associated with baroreceptor nerve terminals. Surprisingly, αENaC subunit could not be demonstrated in nodose ganglia, raising the possibility that γ and βENaC subunits might be associating with an unidentified third channel subunit. This result may underlie the differences in mechanosensitive channel conductance and selectivity previously observed in a variety of tissue types (Sachs and Morris, 1998). Finally, mechanosensory responses, such as puff-induced Ca^{2+} entry in retrogradely labeled nodose cells and baroreflex nerve discharge in response to artery distention, could be reversibly inhibited by amiloride and its analog. Although not demonstrating mechanosensitive gating of DEG/ENaC channels directly, these results do strengthen the evidence that these channels are the basic mechanotransducers in the baroreceptor nerve terminals.

What is the role of the membrane-associated cytoskeleton in gating the DEG/ENaC channels? The Unc-105 mutant in *C. elegans* is characterized by hypercontracted muscle resulting from unabated cation entry. Unc-105 interacts with Let-2, which encodes collagen IVa2. The Unc-105 mutation can be counteracted by mutations in Let-2, further reinforcing the notion that the cytoskeleton is important in the gating of mechanosensitive channels. In humans, X-linked Becker's and Duchenne's muscular dystrophies are associated with a faulty myoplasmic Ca^{2+} handling somehow resulting from the disruption of the cell cytoskeleton (Anderson and Kunkel, 1992). By analogy, recordings of mechanosensitive channels from skeletal muscle from a mouse model of human X-linked muscular dystrophy (*mdx*) exhibit constitutively active channels at rest (Franco and Lansman, 1990) and elevated Ca^{2+} entry (Turner et al., 1991). It will be interesting to see if mutations of the DEG/ENaC channels cause human disorders not previously understood on the molecular level.

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Silencing the Controversy in LTP?

Why has there been such long-term controversy (LTC) over the mechanisms underlying long-term potentiation (LTP)? The inability to resolve this debate may have many sources, including intrinsically empirical as well as sociological factors. Certainly, the regulatory mechanisms underlying modification of transmission in the brain are likely to be complex, and the tools we posses are relatively coarse. In this light, the fact that scientists generally are clever enough to think of mechanistic scenarios that cannot be disproved by existing empirical tools complicates the search. Furthermore, the imbalanced impact of positive results over negative results, or the natural bias of scientists to champion their own point of view, can prolong the discourse. Whatever the source, the field of LTP has been mired with LTC to the point that most consider it a long-term tar pit (LTTP). How does one escape eternal fossilization? It can only be hoped that over time different groups, using different techniques and asking questions related to different aspects of synaptic transmission modulation, will provide the cleansing solvent.

Toward this end, a number of groups have been scouring the biophysical underpinnings of some scenarios proposed to explain LTP in CA1 hippocampus. This month, Gomperts et al. (1998 [this issue of *Neuron*]) address the biophysical basis of "silent" synapses, a sticky issue currently at the fulcrum of the debate over whether LTP is due to a pre- or postsynaptic modification. "Silent" synapses refer to excitatory transmission mediated purely by NMDA receptors (NMDARs): due to the voltage-dependent properties of NMDARs, such transmission will produce no postsynaptic response at resting potentials; hence, it is termed silent. Addition of AMPARs (which are functional at resting potentials) to synapses with only NMDARs was proposed as a possible postsynaptic mechanism to explain the (consistently observed) decrease in synaptic failures during LTP, evidence that is traditionally interpreted as a presynaptic change (Liao et al., 1992). Support for such a process, relying on the difference in variability between AMPAR- and NMDAR-mediated responses, was initially detected by Kullmann (1994). This view was strengthened by direct observations of pure NMDAR-mediated synaptic responses and a conversion of silent synapses to functional synapses during LTP (Isaac et al., 1995; Liao et al., 1995). Thus, a simple postsynaptic model emerged that could largely explain the existing data on LTP, even those data classically interpreted as a change in presynaptic function. If nothing else, this model is attractive because it requires only established intracellular signaling mechanisms. It has been well accepted that postsynaptic processes initiate LTP; now well-established intracellular second messenger mechanisms (such as protein phosphorylation or membrane trafficking) can explain the longer-lasting modification.

However, this model requires the existence of synapses with only NMDARs. While few doubt that pure NMDAR responses exist, an alternative mechanism to the silent synapse hypothesis has been proposed based on a series of experimental findings (reviewed by Kullmann and Asztely, 1998). In this scenario, all excitatory synapses have both AMPA and NMDA receptors. Pure NMDA responses onto cell A are due to the "spillover" of transmitter from a synapse directly contacting cell B. The concentration of transmitter, once it reaches cell A, is sufficient to activate NMDARs but not AMPARs because of their lower affinity for transmitter. Gomperts et al. test this model by examining excitatory transmission in a preparation where an individual neuron is cultured in isolation and makes synapses only on itself. In